Exhibit 8

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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

ARIA DIAGNOSTICS, INC. Plaintiff, v. SEQUENOM, INC., Defendant/ Counterclaim-Plaintiff, v. ARIA DIAGNOSTICS, INC., Counterclaim-Defendant, and ISIS INNOVATION LIMITED, Nominal Counterclaim-Defendant.	Case No. 3:11-cv-06391-SI **DECLARATION OF DR. MARK I. EVANS IN SUPPORT OF SEQUENOM, INC.'S MOTION FOR PRELIMINARY INJUNCTION** Date: April 13, 2012 Time: 9:00 a.m. Place: Courtroom 10, 19TH Floor

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I, Mark I. Evans, declare:

I. INTRODUCTION

1. I am Professor of Obstetrics & Gynecology at Mt. Sinai School of Medicine. I am also President of the Fetal Medicine Foundation of America, President of the International Fetal Medicine and Surgery Society Foundation, and Past President of the Central Association of Obstetricians and Gynecologists. I am also the director of Comprehensive Genetics in New York, an organization specializing in genetic counseling/consultations, prenatal diagnosis, ultrasound, diagnostic procedures such as amniocentesis, chorionic villus sampling, fetal tissue biopsies, fetal therapy, and multiple pregnancy management including fetal reductions.

2. I have been retained by Sequenom, Inc. ("Sequenom") to provide my expert opinions regarding United States Patent No. 6,258,540 ("the '540 patent"). In particular, I have been asked to explain the science in the patent and to provide opinions regarding the meaning of certain terms in the claims of the '540 patent, whether Aria Diagnostics, Inc. ("Aria") has infringed claims 1, 2, 8, 19-22, 24 and 25 of the '540 patent, the validity of the '540 patent, and related matters. I submit this declaration in support of Sequenom's Motion for Preliminary Injunction.

II. SUMMARY OF OPINIONS

3. In my scientific opinion, for the reasons set out in this declaration, Aria's Harmony Prenatal Test™ that utilizes the DANSR™ assay and the FORTE™ algorithm infringes at least claims 1, 2, 8, 19-22, 24 and 25 of the '540 patent.

4. I am informed and understand that a patent is presumed valid. I also understand that Aria has not challenged the validity of the '540 patent in its complaint for a declaratory judgment of non-infringement. If Aria offers any arguments or evidence relating to validity, I reserve the right to respond by way of a supplemental declaration.

5. If Aria is permitted to market the Harmony Prenatal Test™ at all, *i.e.*, if it is not enjoined, and if it markets the test to women with low risk of fetal aneuploidy pregnancies

without a proper clinical validation, it will significantly harm the market for noninvasive aneuploidy testing.

III. QUALIFICATIONS AS AN EXPERT

6. I have worked in the field of prenatal and fetal medicine and diagnosis for over 30 years. A copy of my Curriculum Vitae, including a list of my publications, is attached as Exhibit 1.

7. I earned a Bachelor of Science Magna Cum Laude with special honors from Tufts University in May 1973, and in May 1978 I earned my Doctor of Medicine degree from SUNY Downstate with Distinction in research. From 1978 to 1982, I did my Obstetrics & Gynecology residency at the University of Chicago, and from 1982 to 1984, I did a Medical Genetics fellowship at the National Institutes of Health. I am board certified in Obstetrics & Gynecology and also in Clinical Genetics.

8. From 1984 to 2000, I was a member of the medical school faculty at Wayne State University in Detroit, Michigan rising from Assistant Professor of Obstetrics & Gynecology to the Charlotte B. Failing Endowed Chair and Distinguished Professor of Obstetrics & Gynecology, Chair of Obstetrics & Gynecology, Professor of Molecular Medicine and Genetics, and Professor of Pathology; from 2000 to 2002, I was the Professor and Chairman of Obstetrics & Gynecology at MCP Hahnemann University. I am now Professor at the Mt. Sinai School of Medicine in New York.

9. I have been considered a pioneer in the development of many advances in obstetrics including for prenatal diagnosis, chorionic villus sampling, screening techniques for chromosome abnormalities, and in utero fetal muscle biopsy for Duchenne Muscular Dystrophy. I helped develop the nation's largest AFP (alpha fetoprotein) program for Metpath/Corning/Quest, and in conjunction with the Fetal Medicine Foundation helped develop nuchal translucency screening and training worldwide. In fetal therapy, I developed the method for the first prevention of a birth defect preventing genital masculinization in congenital adrenal hyperplasia, and was part of the team that did the first open fetal surgery for diaphragmatic hernia

and fetoscopic umbilical cord ligation to treat twin reversed arterial perfusion (TRAP) sequence anomalies. I performed the first successful in utero stem cell transplant to cure a baby with Severe Combined Immunodeficiency (SCIDS) – the disease that causes "bubble babies." I have been the acknowledged leader in the development and publishing for the fetal reduction procedure through which the outcomes of multiple pregnancies have been dramatically improved over the last twenty years.

10. I have over 1100 scientific publications including 30 text books. I have been Editor in Chief of *Fetal Diagnosis and Therapy* and on the editorial boards of the *American Journal of Medical Genetics*, *Prenatal Diagnosis*, *Reproductive Medicine* (formerly *J SGI*), and *Journal of Reproductive Medicine*. I have been a medical reviewer for multiple medical journals including the *New England Journal of Medicine, JAMA, Lancet, British Medical Journal*, *American Journal of Obstetrics & Gynecology*, *Obstetrics & Gynecology*, and *British Journal of Obstetrics & Gynecology*. I have also been on the Scientific Advisory Boards of Metpath/Corning Clinical Labs/Quest, and Ikonisys.

11. I lecture regularly as Visiting Professor around the world. I have directed and participated in numerous national and international teaching and research conferences and am rated as one of the top lecturers in Obstetrics & Gynecology.

12. I have had multiple National Institutes of Health (NIH) and other grants including being a principal investigator for the search for fetal cells in maternal blood (NIFTY trial). The collaborative work on fetal cells was the precursor to the now emerging field of noninvasive prenatal diagnosis with the use of free fetal DNA.

13. I have received numerous national and international honors including receiving the President's Award for Achievement from the Society for Gynecologic Investigation, and being elected President of the International Fetal Medicine and Surgery Society twice. I have received awards from Planned Parenthood and the National Organization for Women for work in defending women's rights.

14. I have served on multiple national and international professional committees including the ethics committee of the American College of Obstetricians and Gynecologists and the Board of Directors (as Treasurer) of the International Society of Prenatal Diagnosis. I am currently the President of the International Fetal Medicine and Surgery Society Foundation. I have been President of the Central Association of Obstetricians and Gynecologists.

15. I have appeared on numerous national news programs such as all three American network news shows, 20/20, Turning Point, Nightline, Larry King, specials on Discover, PBS, and foreign networks to explain new technologies, and I am regularly quoted for my own work and to comment on advances by the New York Times, Washington Post, and Wall Street Journal. I have been in Who's Who in America for many years, and have been named by The Best Doctors for Women as one of the top 40 Obstetricians in the United States.

IV. MATERIALS REVIEWED, PRIOR CASES, AND RATE

16. I have reviewed the '540 patent (Exhibit 2 hereto) and its prosecution file history (part of which is attached as Exhibit 3 hereto), and three papers relating to Aria's Harmony Prenatal Test™ (Exhibits 5 to 7 hereto), together with the materials cited herein.

17. A list of the cases in which, during the previous four years, I have testified as an expert at trial or by deposition is included in my resume.

18. I am being compensated at my usual hourly consulting rate of $650 for my work on this case. None of my compensation depends upon the outcome of this case.

19. The opinions set forth in this declaration are based on my personal knowledge gained from my professional experience, education, and review of documents and data referred to in this declaration. I may supplement, refine, or revise my analysis as appropriate, including if additional testimony, documents, or other discovery materials become available. If requested, I will testify at Court hearings and proceedings. I may give a tutorial on the relevant subject matter and use illustrations or other demonstratives to explain and illustrate my opinions. I understand that during the course of these proceedings, additional evidence regarding the details of the Aria Harmony Prenatal Test may be made available to me. I reserve the right to update my analysis,

opinions and conclusions based on any such new information. I also reserve the right to respond to any evidence or arguments that may be offered by Aria.

V. TECHNOLOGICAL BACKGROUND

20. Dr. Dennis Lo's and Dr. James Wainscoat's discovery in 1996-1997 of the presence of cell-free fetal DNA in maternal plasma and serum was a landmark event in the field of prenatal diagnosis.

21. Up to that point, the focus of noninvasive prenatal diagnostic research had been on fetal cells in maternal blood. The discovery that cell-free fetal DNA is detectable in maternal plasma and serum began an entirely new field in the world of prenatal diagnosis.

22. Dr. Lo and Dr. Wainscoat obtained patents for their invention of methods of prenatal diagnosis and analysis, including United States Patent No. 6,258,540, entitled "Non-Invasive Prenatal Diagnosis," which I will refer to in this declaration as the "'540 patent." I understand that Sequenom is asserting claims 1, 2, 8, 19-22, 24, and 25 of the '540 patent against Aria in Sequenom's Motion for Preliminary Injunction. I have attached charts of all the claims asserted as Exhibit 4. Claims 1, 8 and 25 of the '540 patent read as follows:

> 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample and
>
> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.
>
> 8. The method according to claim 1, wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected.
>
> 25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises
>
> obtaining a non-cellular fraction of the blood sample
>
> amplifying a paternally inherited nucleic acid from the non-cellular fraction
>
> and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

23. For clarification, I note that the terms "fetus" and "fetal" are the American spellings of "foetus" and "foetal" respectively, which are the European/UK spellings.

24. In order to explain the pioneering advance that Dr. Lo's and Dr. Wainscoat's discovery represented and to properly understand the foundational '540 patent, it will be helpful first to describe and explain briefly several key scientific concepts and terminologies relating to prenatal diagnosis, human genetics and related topics.

A. BASIC TERMS CONCERNING GENETICS, DNA AND CHROMOSOMES

25. It has been known for thousands of years that organisms inherit traits from their parents, but we only learned of the units of heritability—genes—in 1865. Since then, we have learned that genes are portions of chromosomes, which are made up of DNA.

26. DNA, which stands for **d**eoxyribose **n**ucleic **a**cid, is a molecule that contains the genetic code. DNA, which can form very long strands, is composed of a sugar (deoxyribose) and phosphate backbone with four alternating bases: adenine, cytosine, guanine, and thymine, abbreviated A, C, G, and T. A DNA "sequence" is simply a string of bases; for example: AGCTACG. Each unit of the DNA chain is also known as a "nucleotide" consisting of the sugar, phosphate, and base. DNA usually exists in a double helix composed of two complementary strands of DNA, as famously discovered by Watson and Crick in 1953. In the double helix, As and Ts on opposite strands are paired, as are Gs and Cs. Thus, if one strand has the sequence AATTGGCC, the other strand has the complementary sequence TTAACCGG. There are just over 3 billion base pairs in the haploid human genome. Since we normally have two copies of each chromosome (discussed below) (with the exception of the sex chromosomes), one from mother and one from father, there are really about 6 billion base pairs per individual. All of us have almost exactly half of our DNA maternally inherited and half paternally inherited.

Figure 1. This shows the double-helix structure of DNA with the two strands connected by complementary base pairs.

27. The double-stranded DNA is folded and coiled with various proteins to form a more compact structure: the chromosome. There are 23 pairs of chromosomes that form the human genome. The first 22 are numbered and one of each pair comes from each parent. The last pair are the sex chromosomes. Women have two "X" chromosomes, and men have one "X" and one "Y." The chromosomes are housed in the nucleus of the cell.

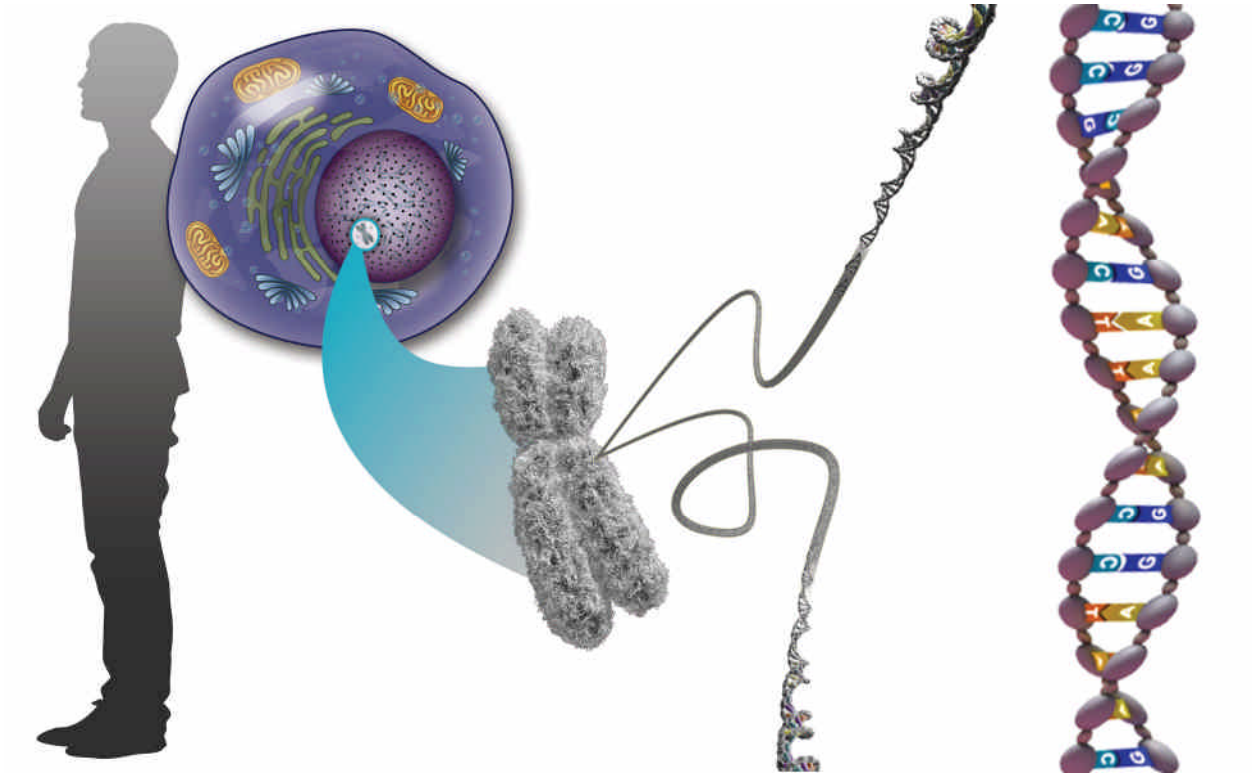


Figure 2. This figure illustrates the human genome that is made up of DNA folded into 23 pairs of chromosomes, all of which are contained in the nucleus of nearly every cell in the human body.

B. ANEUPLOIDIES AND DOWN SYNDROME

28. "Euploidy" is having the normal number of chromosomes. "Aneuploidy" is having an abnormal chromosome count, and usually involves a change in the amount of a single chromosome. "Trisomy" is an aneuploidy in which there are three copies of a chromosome, rather than the normal two ("disomy," also "euploidy" in humans). Down syndrome, in 95% of cases, is caused by trisomy of chromosome 21: affected individuals have three copies of chromosome 21 instead of the normal two copies, which results in a number of physical and mental impairments. In approximately 5% of Down syndrome cases, a chromosomal translocation occurs where an extra chromosome 21 becomes attached (translocated) to another chromosome, in addition to the normal two copies of chromosome 21.

29. Trisomy 21 / Down syndrome can be caused by errors in the process of cell division in the formation of sex cells (sperm and eggs - "gametes"), a process called "meiosis." Meiosis is supposed to yield gametes with exactly half the normal number of chromosomes—22 numbered chromosomes plus a sex chromosome (X or Y). But when the chromosome pairs pull apart to form the gametes, sometimes a pair of chromosome 21 will stick together and end up in a single gamete. Then, when the abnormal gamete fuses with the normal sperm or egg, there is an extra copy of chromosome 21 in the fetus. This sticking together can happen in either parent, but happens much more frequently in the mother.

30. A person or fetus with trisomy 21 or Down syndrome thus inherits one copy of chromosome 21 from their father ("paternally inherited"), one copy of chromosome 21 from their mother ("maternally inherited"), and then a third copy of chromosome 21 from either the father or mother. Whether the additional chromosome 21 is from the mother or the father, there is nevertheless always at least one chromosome 21 inherited from the father, *i.e.*, paternally inherited. This is also true for translocation Down syndrome and for trisomies of all other chromosomes.

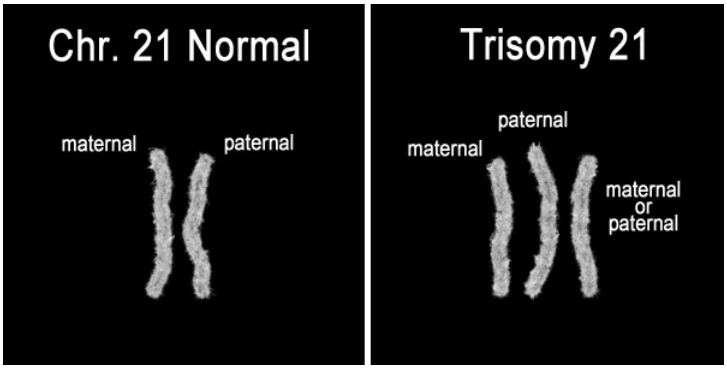


Figure 3. This figure illustrates the inheritance of copies of chromosome 21 in a normal fetus (two copies) and a trisomy 21 fetus (three copies). In both (and all) cases, there is a paternally-inherited copy of chromosome 21.

C. TRADITIONAL PRENATAL INVASIVE TESTING

31. The incidence of fetal trisomies is directly related to maternal age. While the age of the father is generally irrelevant to the risk of fetal abnormalities until at least the age of 50, all of a woman's eggs are made before her birth. As women increase in age, so does the likelihood of a fetal abnormality by aneuploidy. The risk of having a child with Down syndrome increases in a gradual, linear fashion until about age 30 and increases exponentially thereafter. "Historically, maternal age 35 years or older at the time of delivery has been used to identify women at highest risk of having a child with Down syndrome, and these women have been offered genetic counseling and amniocentesis or chorionic villus sampling (CVS)." American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 77 (January 2007).

32. The risks of Down syndrome and any chromosomal abnormality at birth as the age of the mother at birth increases is shown on the following table from Hook (1981):

MATERNAL AGE AT BIRTH	DOWN SYNDROME RISK AT BIRTH	RISK OF ANY CHROMOSOME ABNORMALITY AT BIRTH
20	1/1667	1/526
25	1/1250	1/476
30	1/952	1/384
35	1/385	1/204
38	1/175	1/103
40	1/106	1/65
42	1/64	1/40
44	1/38	1/25

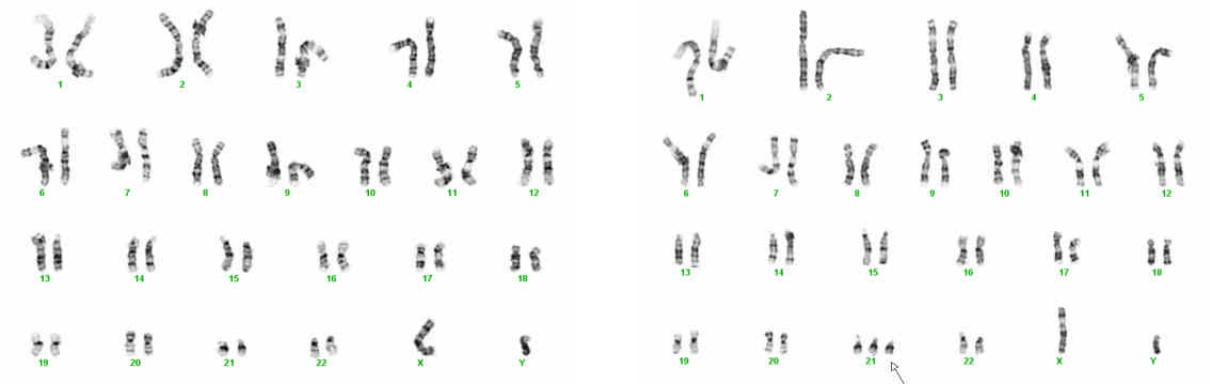
Overall, Down syndrome accounts for about half the risk of fetal abnormalities at birth – being a lower proportion at younger ages and rising. There are other risk factors, for example, couples who already have a baby with Down syndrome have an increased risk of having another baby with the condition. However, despite the fact that the risk for any given 35-year-old is greater than any given 25-year-old, there are actually more Down syndrome babies born to the 25-year-olds because there are many more births to 25-year-olds. As such, the public health issue concerns women of all ages and highlights the need to identify all women at increased risk of having a baby with Down syndrome or other serious disorder regardless of their actual chronological age.

33. There have been screening tests in place over the past 30-plus years to assess the odds that a woman is carrying a fetus with Down syndrome. These screening tests have included over the years various maternal blood tests; first, singly alpha fetoprotein (AFP), then combinations of AFP and human chorionic gonadotropin (hCG), its free β subunit, estriol, and inhibin were added in the second trimester. In the first trimester, pregnancy associated plasma protein A (PAPP-A), free β hCG and multiple ultrasound markers in the first and second trimester such as the nuchal translucency (NT), which is the thickness of the back of the neck, are incorporated into a risk algorithm producing a likelihood ratio which is then multiplied by the *a priori* risk of the mother's age to produce an adjusted risk. Patients who are considered at "high risk" – typically a risk comparable to the risk of a 35-year-old at delivery – can then be offered a

definitive diagnosis by either amniocentesis or chorionic villus sampling. There are literally thousands of publications over the past 30 years detailing the advantages and limitations of the screening tests. All only produce an "odds adjustment," and a definitive answer requires fetal tissue usually by amniocentesis or CVS. Positive results must be followed up with invasive testing, and negative screening results do not necessarily mean that there is a normal number of chromosomes – even the best such tests in practice only have about an 85% detection rate, and false positives are a problem. *See* Evans MI, Hallahan TW, Krantz D, Galen RS: Meta-Analysis of first trimester Down Syndrome screening studies: Free beta hCG significantly outperforms intact hCG in a multi-marker protocol, *American Journal of Obstetrics & Gynecology*, 2007; 196:198-205; Evans MI, Van Decruyes H, Nicolaides KH: Nuchal translucency (NT) measurements for 1st trimester screening: the "price" of inaccuracy, *Fetal Diagnosis & Therapy*, 2007; 22:401-404; Evans MI, Cuckle HS: Biochemical Screening for Aneuploidy, *Expert Reviews in Obstetrics & Gynecology*, 2007; 2:765-774.

34. Invasive prenatal testing and screening has been available for many years. As stated in the '540 patent at column 1, lines 12-17, "Conventional prenatal screening methods for detecting foetal abnormalities and for sex determination traditionally use foetal samples derived by invasive techniques such as amniocentesis and chorionic villus sampling. These techniques require careful handling and present a degree of risk to the mother and to the pregnancy."

35. The traditional way trisomy is detected is to take a cell, visualize the chromosomes by staining, arrange them in order from largest to smallest, and then study them under a microscope. That is called karyotyping:



(a) Normal (b) Down syndrome

Figure 4. This illustrates the results of karotyping to identify the extra copy of chromosome 21 (shown by the arrow) in a fetus with Down syndrome.

36. Karyotyping a fetus requires first obtaining a fetal cell. This is done mostly through amniocentesis or chorionic villus sampling ("CVS"). Both procedures are "invasive." They require an insertion into the mother's body close to the fetus, so that there is an inherent, although small, risk of miscarriage, infection, or bleeding. Many women at high risk of an aneuploid fetus choose not to have these procedures because of their potential problems. The analysis of free fetal DNA as described in the '540 patent allows women to find out without procedure risk whether they do or do not have a fetus with Down syndrome.

37. In amniocentesis, the physician inserts a needle transabdominally into the amniotic sac and extracts fluid, which contains some cells from the fetus. In CVS, the physician biopsies, either transcervically or transabdominally, the chorionic villi, a fetal tissue that eventually becomes the placenta. CVS can be performed earlier in gestation than amniocentesis. It is usually performed at about 11-12 weeks from the last period. Both procedures have risks of causing miscarriage, that is, loss of the fetus. In inexperienced hands, CVS has a higher risk than amniocentesis. Generally, these procedures are performed by high-risk obstetricians using ultrasound guidance to visualize the needle or catheter path to obtain the specimen and reduce the risk of pregnancy loss or causing damage by the procedure. These procedures have been a large

part of my own medical practice for the past 30 years. A noninvasive test that gave the same result that does not require an insertion into the mother's body close to the fetus, such as a blood or urine sample or a cheek swab, would have many advantages.

D. FAILURE OF EARLY ATTEMPTS AT NONINVASIVE PRENATAL TESTS

38. Given the risks of invasive prenatal testing, developing a noninvasive test to replace invasive testing has been a long-held goal in the prenatal diagnosis field.

39. One potentially promising approach was to isolate and use fetal cells which make their way into the maternal bloodstream. This approach was actively investigated from the late 1970's into the 2000's. I was directly involved in this research for over a decade. *See, e.g.*, Bianchi DW, Simpson JL, Jackson LG, Elias S, Holzgreve W, Evans MI, Dukes KA, Sullivan LM, Klinger KW, Bischoff FZ, Hahn S, Johnson KL, Lewis D, Wapner RJ, de la Cruz F. Fetal gender and aneuploidy detection using fetal cells in maternal blood: Analysis of NIFTY I Data, *Prenatal Diagnosis*, 2002; 22:609-615; Zheng UL, Zhen DK, Berry SM, Wapner RJ, Evans MI, Copeland D, Williams JM, Bianchi DW. Search for the optimal fetal cell antibody I, *Human Genetics*, 1997; 100:35-42; Kilpatrick MW, Tafas T, Evans MI, Strinkovsky L, Jackson LG, Tsipouras P. Getting fetal cells in maternal blood to work: eliminating the false positive XY signals in XX pregnancies, *American Journal of Obstetrics & Gynecology*, 2004; 190,1571-81. Seppo A, Frisova V, Ichetovkin I, Kim Y, Evans MI, Antsaklis A, Nicolaides KH, Tafas T, Tsipouras P, Kilpatrick MW: Detection of circulating fetal cells utilizing automated microscopy: potential for non-invasive prenatal diagnosis of chromosomal aneuploidies, *Prenatal Diagnosis*, 2008; 28:815-821. *See also*, Lo YMD. et al., Prenatal sex determination by DNA amplification from maternal peripheral blood, *Lancet*, 1989; 2:1363-65; Lo YMD, et al, Two-way cell traffic between mother and fetus: biologic and clinical implications, *Blood*, 1996; 88:4390-95; Simpson JL & Elias S, Isolating foetal cells from maternal blood: advances in prenatal diagnosis through molecular technology, *JAMA*, 1993; 270:2357-61. However, despite years of trying by multiple methods, no one was ever able to achieve acceptable success and accuracy. There were many problems including that fetal cell techniques are time-consuming, expensive, and still inaccurate.

40. To achieve prenatal diagnosis using fetal cells in maternal blood, it is important that pure fetal cells be isolated. Cheung et al., Prenatal diagnosis of sickle cell anemia and thalassemia by analysis of foetal cells in maternal blood, *Nature Genetics*, 1996; 14: 264-68. However, this has been a very challenging problem that is still largely unsolved after decades of work by scientists. The protocol involved taking maternal blood, applying density gradient separation of mononuclear cells, removing those cells, washing them, enriching fetal cells by magnetic activated cell sorting using anti-transferring receptor antibody, and then smearing those cells onto a slide for identification of fetal cells by immuno-staining with anti-fetal or embryonic hemoglobin antibodies. For some methods, the fetal cells identified by the stain then had to be manually scraped off the slide with a glass needle controlled by a micromanipulator under a microscope, and then subjected to polymerase chain reaction ("PCR") analysis and probing. *Id*. The process had many steps and was labor-intensive. Other methods, including automated fetal cell identification, were an improvement, but they could not reliably separate out true fetal cells from maternal ones as there is no pure fetal antigen against which to stain.

41. Ultimately, neither approach, using fetal cells or the other noninvasive screening measurements described above, has proved sufficiently successful or reliable to replace invasive testing. Dr. Lo's and Dr. Wainscoat's discovery of the presence of cell-free fetal DNA in maternal plasma and serum – discussed below in Section VI – was a pioneering breakthrough for noninvasive prenatal testing.

E. SEQUENCING AND DETECTING NUCLEIC ACIDS

42. As described earlier, nucleic acids are made of strings of nucleotides with bases A, C, G, or T. The sequence of bases, such as AATCGTAC, can be determined by various "sequencing" methods. In 1997, various methods for sequencing were known. Since 1997, improved techniques for sequencing have been developed, but the concept of sequencing, that is, identifying the order of the bases, is the same. The nucleic acids are usually amplified prior to sequencing. Various methods of amplification were known back in 1997, but the most common is called the "polymerase chain reaction," or "PCR," which was invented in the 1980's. PCR uses

short DNA "primers," which are short DNA sequences complementary to regions flanking the sequence of interest. Those primers are added to the sample, and bind to their targets. DNA polymerase, the enzyme which builds DNA strands, then recognizes the primers and fills in the complementary strand from the primer on. The process is repeated for as many cycles as are necessary, each time doubling the amount of the sequence of interest.

43. Although everyone's genomes are very similar, they are not identical. Such is the basis of genetic diagnosis. Variations in the DNA of a genome come in different types, such as substitutions, insertions or deletions of nucleotides, and in many cases these variations (or "alleles") have no effect on a person. One type of variation is a "single nucleotide polymorphism" or "SNP," which is a change of a single base at a particular position, or "locus," so that, for example, some people have an "A" (*i.e.*, the "A" allele) and others have a "C" (*i.e.*, the "C" allele) at a specific locus on a chromosome. The "minor allele frequency" refers to the frequency at which the less common allele occurs at a locus in a given population. SNPs can be used to distinguish DNA from different individuals. For example, SNPs are used in DNA analysis of blood or other fluids left at crime scenes. Once a nucleic acid has been sequenced, the sequence can then be compared to known sequences to determine, for example, which chromosome the DNA came from or the nature of any polymorphisms in that nucleic acid sequence.

F. BLOOD, PLASMA AND SERUM

44. Whole blood is living tissue made up of liquid and solids. The liquid part, called plasma, is made of water, salts and protein; in other words it is "non-cellular." Approximately half of our blood is plasma – it is the fluid in which blood cells are suspended. The solid part of our blood contains red blood cells, white blood cells, and platelets. Red blood cells deliver oxygen from the lungs to the tissues and organs. White blood cells fight infection and are part of the body's defense system. Platelets help blood to clot. Blood cells have a short life span, and the body makes new ones. Red blood cells live about 120 days, platelets 6 days, and white cells

less than a day. Serum is blood plasma without the clotting factors, that is, whole blood minus both the cells and the clotting factors.

VI. THE INVENTION OF THE '540 PATENT

45. In around 1996-1997, Drs. Lo and Wainscoat, who had already been working in the field of prenatal diagnosis for many years, discovered that fetal DNA is detectable in maternal serum or plasma samples. This was a landmark discovery for the prenatal diagnosis field.

46. This invention has been widely recognized both in the scientific community and in the scientific literature. For example, Dr. Lo has been elected to the Fellowship of the Royal Society, which is "made up of the most eminent scientists, engineers and technologists from the UK and the Commonwealth. Fellows and Foreign Members are elected for life through a peer review process on the basis of excellence in science," according to the website of the Royal Society.

47. Dr. Lo has also won many prizes and been honored for his work, including, I understand, the following:

- The AACC (American Association for Clinical Chemistry)-NACB (National Academy of Clinical Biochemistry) Award for Outstanding Contributions to Clinical Chemistry in a Selected Area of Research (2012). This is a very prestigious award that "recognizes especially meritorious research contributions by an individual in a specific area of clinical chemistry. The clinical chemists who have received this award have achieved national and international status for their pioneering efforts in an area of research considered fundamental to the science and have been considered among the world's foremost experts in that specific discipline." Among previous winners are Nobel Prize winners Kary Mullis, the inventor of PCR, and Dr. Rosalyn Yalow, who developed the radioimmunoassay technique;
- Silver Bauhinia Star, Hong Kong SAR Government (2011);
- Sir David Todd Orator, Hong Kong Academy of Medicine (2011), which I understand is the most prestigious lecture of the Hong Kong Academy of Medicine;
- Fulbright Distinguished Scholar Award (2009-10);
- Chemical Pioneer Award, American Institute of Chemists (2006);

- Cheung Kong Scholars Achievement Award, Ministry of Education, China (2006);
- U.S. National Academy of Clinical Biochemistry Distinguished Scientist Award (2006);
- International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) - Abbott Award for Outstanding Contribution to Molecular Diagnostics (2006);
- Croucher Senior Medical Research Fellowship (2006). I understand that the election to a Croucher Senior Fellowship is a very prestigious award for academics working in Hong Kong;
- State Natural Science Award (Class II), People's Republic of China (2005). I understand that the State Natural Science Awards, given by the State Council of China, are the most prestigious awards in natural science in China;
- Honoree, Outstanding Young Persons of the World Junior Chamber International (2001);
- Leader of the Year Award, Technology Category organised by Sing Tao Daily, Hong Kong iMail and CNBC (2000);
- Awardee, Outstanding Young Person Selection (Hong Kong) (2000);
- Professors' Prize, Association of Professors of Academic Departments of Chemical Pathology (2000).

48. In addition, Dr. Lo has been elected to honorary Professorships:

- Honorary Professor, Nanjing Medical University, China;
- Honorary Professor, Sun Yat-sen University, China.

49. I understand Dr. Lo is Associate Editor, *Clinical Chemistry*, which is the official journal of the American Association for Clinical Chemistry, and is an Editorial Board Member of the following scientific journals: *Journal of Pathology, American Journal of Hematology, Prenatal Diagnosis, Disease Markers,* and *Chimerism*.

50. I understand Dr. Lo is a reviewer for the following journals: *Nature, Science, New England Journal of Medicine, Lancet, Nature Medicine, Science Translational Medicine, Proceedings of the National Academy of Sciences (USA), Journal of the American Medical Association, Journal of Clinical Investigation, Cancer Research, American Journal of Human Genetics, Nature Protocols, American Journal of Obstetrics & Gynecology, Clinical Cancer Research, Human Genetics, Molecular Human Reproduction,* and *Prenatal Diagnosis*.

51. He has also been invited to lecture and speak at many international conferences on the topic of noninvasive prenatal diagnosis, and the presence and detection of cell-free fetal nucleic acids in maternal plasma.

52. In short, it is clear that Dr. Lo has received wide-spread recognition for his ground-breaking invention and for, as the Royal Society described it, "creating a paradigm shift in non-invasive prenatal diagnosis."

53. Drs. Lo and Wainscoat have also received recognition in the scientific literature, including the exciting nature of their discovery. For example, in 2000, researchers in the field wrote: "A very recent exciting discovery has been that free extracellular fetal DNA can be detected in the plasma and serum of pregnant women." Holzgreve W & Hahn S, Fetal cells in cervical mucus and maternal blood, *Bailliere's Clinical Obstetrics and Gynaecology*, 2000; 14:4:709-22. *See also* below in paragraph 71.

54. Drs. Lo and Wainscoat filed patent applications relating to their invention. One of those patent applications became the '540 patent which is at issue in this case.

A. THE '540 PATENT

55. I have reviewed the '540 patent (Exhibit 2). I have also reviewed the prosecution file history for the '540 patent (part of which is attached as Exhibit 3), which I understand is a collection of the communications and materials exchanged between patent counsel for the patent applicants and the United States Patent and Trademark Office ("USPTO") during the prosecution of the '540 patent.

56. Based upon my review of the '540 patent and its file history, I understand the following. The earliest patent application filed by Drs. Lo and Wainscoat for their invention was an application filed in the United Kingdom Patent Office on March 4, 1997, UK Patent Application No. GB 9704444, entitled "Non-Invasive Prenatal Diagnosis." One year later, on March 4, 1998, Drs. Lo and Wainscoat filed an international patent application, PCT/GB98/00690, which was subsequently filed with the USPTO as U.S. Patent Application No.

09/380,696. On July 10, 2001, this U.S. Patent Application issued as U.S. Patent No. 6,258,540, *i.e.*, the '540 patent, which is the patent asserted by Sequenom in this case.

57. The '540 patent describes the invention by Drs. Lo and Wainscoat of methods utilizing their landmark discovery that cell-free fetal DNA is detectable in maternal serum or plasma.

58. The '540 patent first describes the "Background of the Invention," including invasive and noninvasive screening methods for detecting fetal abnormalities, which I have explained above, and the recent "use of plasma or serum-derived DNA for molecular diagnosis" and "non-invasive cancer diagnosis by detection of K-ras and N-ras gene mutations using PCR-based techniques." (Exhibit 2, '540 patent at 1:10-46.)

59. It then sets out the "Summary and Objects of the Invention," stating that:

> It has now been discovered that foetal DNA is detectable in maternal serum or plasma samples. This is a surprising and unexpected finding; maternal plasma is the very material that is routinely discarded by investigators studying non-invasive prenatal diagnosis using foetal cells in maternal blood. The detection rate is much higher using serum or plasma than using nucleated blood cell DNA extracted from a comparable volume of whole blood, suggesting that there is enrichment of foetal DNA in maternal plasma and serum. In fact, the concentration of foetal DNA in maternal plasma expressed as a % of total DNA has been measured as from 0.39% (the lowest concentration measured in early pregnancy), to as high as 11.4% (in late pregnancy), compared to ratios of generally around 0.001% and up to only 0.025% for cellular fractions (Hamada et al 1993). It is important that foetal DNA is found in maternal plasma as well as serum because this indicates that the DNA is not an artefact of the clotting process. ('540 patent at 1:50-67.)

60. The specification goes on to state that:

> This invention provides a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample. The invention thus provides a method for prenatal diagnosis. ('540 patent at 2:1-5.)

61. The specification explains that "prenatal diagnosis" as used in the patent "covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or to the quality or quantity of the foetal DNA in the maternal serum or plasma.

Included are sex determination, and detection of foetal abnormalities which may be for example chromosomal aneuploidies or simple mutations." ('540 patent at 2:6-12.)

62. The specification then explains how to perform the invention. It addresses how to prepare the serum or plasma sample, how to extract the nucleic acids, and how to amplify the foetal DNA sequences (using "standard nucleic acid amplification systems… including PCR."). ('540 patent at 2:19-48.)

63. The specification states that "[t]he method according to the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother and which may be for example genes which confer a disease phenotype in the foetus." It then describes three "Examples." ('540 patent at 2:49-3:24.)

64. Next, the specification describes that "[t]he plasma or serum-based non-invasive prenatal diagnosis method according to the invention can be applied to screening for Down's Syndrome and other chromosomal aneuploidies" and describes two ways to achieve this. ('540 patent at 3:25-51.) One way is based on the demonstration by Drs. Lo and Wainscoat "that the level of foetal DNA in maternal plasma and serum is higher in pregnancies where the foetus has a chromosomal aneuploidy than in normal pregnancies." As a result, "[q]uantitative detection of foetal nucleic acid in the maternal plasma or serum e.g. a quantitative PCR assay, can be used to screen pregnant women for chromosomal aneuploidies." ('540 patent at 3:30-43.) In other words, the specification describes a quantitative approach for detecting foetal nucleic acid and hence aneuploidy.

65. Another quantitative approach described in the specification involves "quantitation of foetal DNA markers on different chromosomes." ('540 patent at 3:45-45.) The '540 patent explains that: "For example, for a foetus affected by Down's Syndrome the absolute quantity of foetal chromosomal 21-derived DNA will always be greater than that from the other chromosomes…" ('540 patent at 3:45-49.) The specification then states that the "recent development of very accurate quantitative PCR techniques… facilitates this type of analysis." ('540 patent at 3:49-51.)

66. Thus, the '540 patent describes several ways that fetal chromosomal aneuploidies may be detected using cell-free fetal DNA.

67. The specification then sets out five examples: Example 1 "Analysis of foetal DNA for sex determination;" Example 2 "Quantitative analysis of foetal DNA in maternal serum in aneuploid pregnancies;" Example 3 "Non-invasive prenatal determination of foetal RhD status from plasma of RhD-negative pregnant women;" Example 4 "Elevation of foetal DNA concentration in maternal serum in pre-eclamptic pregnancies;" and Example 5 "Quantitative analysis of foetal DNA in maternal plasma and serum." ('540 patent at 4:9-19:8.)

68. Then, after a list of references and a listing of several nucleic acid sequences referenced in the specification, the '540 patent sets out 27 claims of which three – claims 1, 24, and 25 – are "independent" claims, which I understand are claims that do not refer to any other claims. The other 24 claims are "dependent" claims that all refer to other claims.

69. As recognized by the examiner in Dr. Lo's international patent application, "While it is true that the prior art already considered the possibility of diagnosing cancer by detecting tumour specific DNA mutations in the blood plasma fraction, there is no scientifically sound reason to believe that a skilled person would have automatically carried over this prior knowledge to the situation of prenatal diagnostic markers." December 16, 1998, International Preliminary Examination Report, which is included in the '540 patent file history.

70. One reason for this is that "the traditional teaching" was "that the placenta forms an impermeable barrier." *See* Bianchi DW, Circulating Fetal DNA: Its Origin and Diagnostic Potential—A Review, *Placenta*, 2004; 25 Supplement A, Trophoblast Research, Vol. 18, S93-94. While researchers knew that a very small number of fetal cells escaped the placenta, it was not known that cell-free DNA was present in the maternal plasma in detectable quantities. Indeed, despite extensive work in detecting DNA from fetal cells in maternal blood, no cell-free fetal DNA had been detected before Dr. Lo's discovery, and many investigators on many research projects – myself included – discarded the plasma fraction, because nobody thought that fetal cell-free DNA would be present. Lo YMD et al., Presence of fetal DNA in maternal plasma and

serum, *Lancet*, 1997; 350: 485–487. Even Dr. Lo did not know how the fetal DNA got into the maternal circulation; he noted that "Possible mechanisms include cell lysis resulting from physical and immunological damage, and developmentally regulated apoptosis of certain fetal tissues." Lo YMD et al., Presence of fetal DNA in maternal plasma and serum, *Lancet*, 1997; 350: 485–487. Those mechanisms may differ substantially from the mechanisms which put tumor DNA into the blood—mechanisms which at the time were called "enigmatic." Mulcahy HE et al., Cancer and mutant DNA in blood plasma, *Lancet*, 1996; 348:628. The mechanism for creating a high percentage of tumor DNA in plasma "could perhaps be due to greater access to the vasculature in [the cancer type of interest] so that the DNA has more ready access to the circulation." Chen XQ et al., Microsatellite alterations in plasma DNA of small cell lung cancer patients, *Nature Medicine*, 1996; 2:1033-35. Current thinking suggests that the placenta, which is of fetal origin, may likely be the source of much of the free fetal DNA in maternal circulation.

71. Researchers in the field called Dr. Lo's discovery of cell-free fetal DNA in maternal plasma "one of the most exciting discoveries made in recent years." Hahn S & Holzgreve W, Prenatal diagnosis using fetal cells and cell-free DNA in maternal blood: what is currently feasible? *Clinical Obstetrics and Gynecology*, 2002; 45:649-56. Other papers by researchers in the field made similar comments: "A very recent exciting discovery has been that free extracellular fetal DNA can be detected in the plasma and serum of pregnant women." Holzgreve W & Hahn S, Fetal cells in cervical mucus and maternal blood, *Bailliere's Clinical Obstetrics and Gynaecology*, 2000; 14:4:709-22; "The recent discovery of high concentrations of fetal DNA in maternal plasma represents a promising non-invasive approach to prenatal diagnosis." Pertl B & Bianchi DW, Fetal DNA in Maternal Plasma: Emerging Clinical Applications, *Obstetrics and Gynaecology*, 2001; 98:483-490; "The recent demonstration that fetal DNA can be found in easily detectable quantities in maternal plasma has provided new possibilities for non-invasive prenatal testing." Uitto J et al., Probing the fetal genome: progress in non-invasive prenatal diagnosis, *Trends in Molecular Medicine*, 2003; 9:239-243.

72. It may be helpful to illustrate the effect that the small fraction of cell-free fetal DNA in the mother's plasma has on the detection of chromosome 21. Consider, for example, that in a plasma sample the cell-free fetal DNA is 10% of the total cell-free DNA, the other 90% being the mother's. If "A" is the total amount of chromosome 21 in a euploid sample (with the normal 2 copies of chromosome 21), then the euploid fetus will contribute 0.1A of chromosome 21, and the mother will contribute 0.9A – for a total amount of chromosome 21 of A. If, however, the fetus has trisomy 21 (*i.e.*, it has 3 copies of chromosome 21), then the fetus will contribute 0.15A of chromosome 21, with the mother still contributing 0.9A – for a total amount of chromosome 21 of 1.05A. Thus, the amount of chromosome 21 in a plasma sample from a pregnant mother only increases from 1.00 (with a euploid fetus) to 1.05 (with a trisomy 21 fetus). This is a relatively small increase in chromosome 21 to detect.

B. PROSECUTION OF THE '540 PATENT

73. The completed U.S. patent application was filed by Drs. Lo and Wainscoat with the USPTO on November 29, 1999. The first "Office Action" by the USPTO is dated April 18, 2000. This Office Action rejected all 26 then pending claims on a number of grounds. On September 15, 2000, the applicants responded to the grounds of rejection and amended several of the claims. On November 2, 2000, the USPTO rejected all the pending claims of the application. On December 27, 2000, the applicants amended the claims "in accordance with the Examiner's suggestions made on October 26, 2000," apparently during a telephone interview between the applicants' patent counsel and the Examiner, and responded to the grounds of rejection. On January 23, 2001, the USPTO issued a Notice of Allowability, stating that the amended claims were allowable. As part of the Notice of Allowability, the Examiner proposed amendments to the claims which added an amplification step to the independent claims. The applicants apparently had approved the Examiner's amendments during a telephone interview on January 20, 2001. The Notice of Allowability included a statement of the Examiner's reasons for allowance, as follows:

> The following is an examiner's statement of reasons for allowance.
>
> The claims are drawn to a method of detecting paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, by amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.
>
> The closest prior art is directed to detecting alterations in plasma DNA for diagnosing and or monitoring the development of DNA (Stroun et al GB2299166, September 1996). The art also teaches detecting fetal cells in maternal blood and performing diagnostic tests on the blood. However, the art does not teach nor reasonably suggest that nucleic acid of fetal origin is present in maternal serum or plasma.

74. The '540 patent issued on July 10, 2001.

VII. THE LEVEL OF ORDINARY SKILL IN THE ART

75. As discussed above, the '540 patent relates to methods of noninvasive prenatal diagnosis. The arts most relevant to the '540 patent are fetal medicine, prenatal testing and diagnosis, genetics, molecular biology, and biochemistry. I understand that in considering the level of ordinary skill in the field that someone would have had at the time of the invention of the '540 patent, one should consider any relevant facts including the following: the levels of education and experience of persons working in the field; the types of problems encountered in the field; and prior art solutions to those problems.

76. Persons working in the field of prenatal diagnosis usually have medical and/or advanced scientific degrees with a specialty or emphasis in fetal medicine/science, usually with a background or experience in genetics and a knowledge of molecular biology and biochemistry.

77. The types of problems encountered in prenatal diagnosis in the mid-to-late 1990's included problems and risks associated with invasive prenatal diagnostic methods of amniocentesis and CVS and problems of detecting fetal cells in maternal blood. As explained above, these problems with both invasive and noninvasive procedures had not been solved by the time of the present invention by Drs. Lo and Wainscoat.

78. Taking into account these factors, in my opinion, a person of ordinary skill in the art relating to the '540 patent at the time of the invention would have a degree in medicine (or an

advanced degree in a related field) with knowledge of genetics, molecular biology and biochemistry, including two years of practical experience in prenatal diagnosis.

79. I understand that the priority date identified on the '540 patent is March 4, 1997. As I have a degree in medicine, board certification in Obstetrics & Gynecology and in Clinical Genetics, and was an experienced practitioner, researcher, and scientist in the field of prenatal diagnosis for many years prior to that date, I consider myself to be one of skill in the art in the subject matter of this patent.

VIII. LEGAL STANDARDS FOR CLAIM CONSTRUCTION AND INFRINGEMENT

80. In reaching my opinions, I have been informed and understand that the following legal principles apply to (i) "claim construction," that is, determining the meaning of the words in the claims of the '540 patent, and (ii) infringement, that is, determining whether the Aria Harmony Prenatal Test infringes the asserted claims of the '540 patent.

81. I am informed and understand that the claims of a patent define the invention. The courts determine the meaning of disputed claim terms from the perspective of a person of ordinary skill in the art at the time the patent is filed. The person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification. The court looks to the following public sources to determine what a person of skill in the art would have understood the claim language to mean: so-called "intrinsic evidence," which are the words of the claims themselves, the remainder of the specification, the prosecution history, and prior art cited during prosecution; and so-called "extrinsic evidence," such as expert testimony, inventor testimony, dictionaries, and scientific treatises, concerning relevant scientific principles, the meaning of technical terms, and the state of the art.

82. I am further informed and understand that claim terms are generally given their ordinary and customary meaning to a person of ordinary skill in the art. When construing claim terms, I am informed and understand that the court first looks to sources in the "intrinsic" record. First, the claims themselves provide substantial guidance as to the meaning of particular claim

terms. Second, the claims must be read in view of the specification, of which they are a part. The specification is usually dispositive, as it is the single best guide to the meaning of a disputed term. Third, the court should consider the patent's prosecution history, which is the record of proceedings before the Patent and Trademark Office ("PTO") and includes the prior art cited during the patent examination. However, because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes. I am further informed and understand that if the intrinsic evidence resolves the ambiguity in the disputed claim terms, then it is not necessary to consider extrinsic evidence. If ambiguities in the claim terms remain, however, courts may consider extrinsic evidence.

83. I am further informed and understand that while reference to the specification may aid in understanding the meaning of a claim term, it is improper to import the specification into a claim limitation if it is not part of the claim. Claims must be interpreted in view of the specification without unnecessarily importing limitations from the specification into the claims.

84. As to infringement, I am informed and understand that in order to determine if an accused product or process infringes a claim of a patent, a two-step process must be followed. First, the asserted claims must be properly construed to determine their meaning and scope, in accordance with the principles set out above. Second, the claims as properly construed, must be compared to the accused product or process. The second step is a factual determination of whether the claims cover the accused product or process. I am informed and understand that in order to infringe a patent claim, every limitation of the claim must be found in (*i.e.*, "read on") the accused process.

85. I have applied these legal principles in reaching my opinions.

IX. INFRINGEMENT ANALYSIS

86. My infringement analysis is set out below on a claim by claim basis. For each of the asserted claims, I have set out the limitations of the claims as headings. I then give my opinion as to how one of ordinary skill in the art would understand that limitation, and the bases

and reasons I believe Aria's Harmony Prenatal Test™ that utilizes the DANSR™ assay and the FORTE™ algorithm, meets (or infringes) those limitations. I have also attached claim charts as Exhibit 4 comparing the asserted claims of the '540 patent with the Aria processes as described in Aria's publications dated January 6, 2012, and January 25, 2012.

87. I base my infringement analysis of Aria's Harmony Prenatal Test™ on the following papers published on-line in the journals *Prenatal Diagnosis* and *American Journal of Obstetrics and Gynecology* ("AJOG"), in January 2012, namely:

(1) Selective analysis of cell-free DNA in maternal blood for evaluation of fetal trisomy, Sparks AB et al., *Prenatal Diagnosis*, 2012; 32:1–7. (hereafter "Aria PD Publication") (Exhibit 5.)

(2) Non-invasive Prenatal Detection and Selective Analysis of Cell-free DNA Obtained from Maternal Blood: Evaluation for Trisomy 21 and Trisomy 18, Sparks AB et al., *American Journal of Obstetrics and Gynecology*, 2012; doi: 10.1016/j.ajog.2012.01.030. (hereafter "Aria AJOG Publication") (Exhibit 6.)

(3) Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18, Ashoor G et al., *American Journal of Obstetrics and Gynecology*, 2012; doi: 10.1016/j.ajog.2012.01.029. (hereafter "Ashoor") (Exhibit 7.)

88. I also base my infringement analysis on Aria's Press Release dated February 6, 2012, entitled "Aria Diagnostics Announces Name of New Non-Invasive Prenatal Assay – Harmony Prenatal Test™ – and Publication of Study on Specimen Transport." (Exhibit 8.) In this press release, Aria states, among other things:

> Aria Diagnostics, a molecular diagnostics company, today announced that its new prenatal test has been named the Harmony Prenatal Test™. The test is a directed noninvasive approach to cell-free DNA (cfDNA) analysis in maternal blood to detect common trisomies linked to genetic disorders.
>
> …
>
> The Harmony Prenatal Test utilizes new technology which couples innovative biochemistry, DANSR™, and a proprietary algorithm, FORTE™, to efficiently analyze patients' blood samples.

89. This press release confirms that Aria's Harmony Prenatal Test utilizes both the DANSR assay and the FORTE algorithm, which are the two processes described in the Aria AJOG Publication.

90. It is my opinion that Aria has infringed at least claims 1, 2, 8, 19-22, 24, and 25 of the '540 patent, which are the claims that Sequenom has asserted in its Motion for Preliminary Injunction. I understand that Sequenom has also reserved the right to assert other claims against Aria. Although I have not addressed any such other claims, I may do so if requested by Sequenom. As I explain below, in my opinion, all of the words in the claims of the '540 patent have their ordinary and customary meaning to one of ordinary skill in the art and, in fact, are reasonably understandable even to an educated lay person.

A. CLAIM 1

1. "1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises"

91. I understand that this paragraph is a "preamble" and is therefore generally not a limitation of the claim. I also understand that "comprises" means "includes, but is not limited to." If this paragraph were, however, to be construed as a limitation of the claim, then the person of ordinary skill in the art would understand the terms in this limitation as follows.

92. The person of ordinary skill in the art would understand the term "nucleic acid" does not require construction and has its ordinary and customary meaning of "a chain of nucleotides." The '540 patent specification states: "The nucleic acid detected in the method according to the invention may be of a type other than DNA e.g. mRNA." ('540 patent at 2:16-18.)

93. The person of ordinary skill in the art would understand the term "paternally inherited nucleic acid of fetal origin" to have its ordinary and customary meaning of "a nucleic acid that originated from the fetus and which was inherited from the father."

94. The person of ordinary skill in the art would understand the term "detecting" to have its ordinary and customary meaning and does not need to be construed. The Merriam-Webster On-line Dictionary defines "detect" as follows:

> transitive verb
>
> 1: to discover the true character of
>
> 2: to discover or determine the existence, presence, or fact of <*detect* alcohol in the blood>

The second definition is consistent with how "detect" is used in the '540 patent. Thus, if a construction for "method for detecting" is required, it means a "method for discovering or determining the existence, presence, or fact of."

95. Thus, the person of ordinary skill in the art at the time of the invention would understand "a method for detecting a paternally inherited nucleic acid of fetal origin" to mean "a method for discovering or determining the existence, presence, or fact of, a nucleic acid that originated from the fetus and which was inherited from the father."

96. The person of ordinary skill in the art at the time of the invention would also understand that a "maternal serum or plasma sample" would have its ordinary and customary meaning of "a sample of a portion of blood taken from the mother; the liquid, non-cellular portion made of water, salts, and protein is called plasma, and when the plasma's clotting factors are removed, it is called serum."

97. The Aria Harmony Prenatal Test meets this preamble description. As stated in the Aria Press Release and in the Aria AJOG Publication, the Aria test "is a directed noninvasive approach to cell-free DNA (cfDNA) analysis in maternal blood to detect common trisomies linked to genetic disorders… [that] couples innovative biochemistry, DANSR™, and a proprietary algorithm, FORTE™, to efficiently analyze patients' blood samples." (Aria Press Release.) As explained in more detail below, the Harmony Prenatal Test detects a paternally inherited nucleic acid of fetal origin using a plasma sample from a pregnant female.

2. "amplifying a paternally inherited nucleic acid from the serum or plasma sample and"

98. The person of ordinary skill in the art would understand "amplifying" to have its ordinary and customary meaning and does not require construction. If a construction were required, the person of ordinary skill in the art would understand "amplifying" to mean "increasing the amount by making copies." This is consistent with the use of the term "amplifying" in the patent specification. The '540 patent specification states: "An amplification of foetal DNA sequences in the sample is normally carried out. Standard nucleic acid amplification systems can be used, including PCR, the ligase chain reaction, nucleic acid sequence based amplification (NASBA), branched DNA methods, and so on. Preferred amplification methods involve PCR." ('540 patent at 2:43-48.)

99. As set out above, the person of ordinary skill in the art would also understand "paternally inherited nucleic acid" to mean "a nucleic acid that originated from the fetus and which was inherited from the father."

100. This claim limitation is practiced by the Aria Harmony Prenatal Test. As stated in the Aria AJOG publication under the heading "DANSR assay":

> We designed DANSR assays against loci in the human genome as previously described. **To assess chromosome proportion, we designed assays against 576 non-polymorphic loci on each of chr18 and chr21**, where each assay consisted of three locus specific oligonucleotides: a left oligo with a 5' universal amplification tail, a 5' phosphorylated middle oligo, and a 5' phosphorylated right oligo with a 3' universal amplification tail. **To assess fetal fraction, we designed assays against a set of 192 SNP-containing loci on chr1-12**, where two middle oligos, differing by one base, were used to query each SNP. SNPs were optimized for minor allele frequency in the HapMap 3 dataset (http://hapmap.ncbi.nlm.nih.gov/). Oligonucleotides were synthesized by IDT and pooled together to create a single multiplexed DANSR assay pool.

Aria AJOG Publication at 6 (emphasis added). The Aria AJOG Publication further explains:

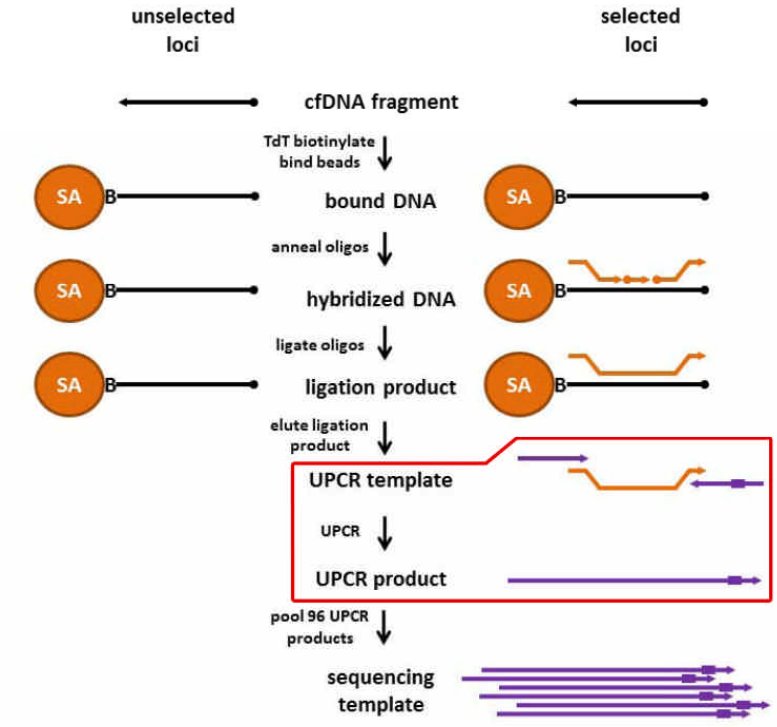
> **8mL blood per subject was collected** into a Cell-free DNA tube (Streck) and stored at room temperature for up to 3 days. **Plasma was isolated from blood** via double centrifugation and stored at -20C for up to a year. **cfDNA was isolated from plasma** using Viral NA DNA purification beads (Dynal), biotinylated, immobilized on MyOne C1 streptavidin beads (Dynal), and annealed with the multiplexed DANSR oligonucleotide pool. Appropriately hybridized oligonucleotides were catenated with Taq ligase, eluted from the cfDNA, and **amplified** using universal PCR primers. PCR product from 96

> independent samples was pooled and used as template for cluster amplification on a single lane of a TruSeq v2 SR flow slide (Illumina). …

See Aria AJOG Publication at 7 (emphasis added).

101. As this excerpt states, the cfDNA, *i.e.*, cell-free nucleic acid, was isolated from the pregnant female's plasma sample. This isolated nucleic acid is a mixture of both nucleic acid from the mother and nucleic acid from the fetus. The nucleic acid from the fetus is made up of nucleic acid that was inherited from the father and nucleic acid that was inherited from the mother. The isolated nucleic acid therefore contains "paternally inherited nucleic acid of fetal origin," as well as maternally inherited nucleic acid of fetal origin, and the mother's own nucleic acid.

102. As this excerpt further describes, the cell-free nucleic acid – including paternally inherited nucleic acid of fetal origin – is amplified: "Appropriately hybridized oligonucleotides were catenated with Taq ligase, eluted from the cfDNA, and **amplified** using universal PCR primers." This is also illustrated in Figure 1 of the Aria AJOG Publication headed "Schematic of DANSR assay," shown below:



This figure illustrates how the cfDNA at the selected loci is amplified. The box above identifies the amplification using universal PCR. *See* also Aria PD Publication, Figure 1.

103. Accordingly, the "amplification" step of claim 1 is met by the Aria Harmony Prenatal Test.

3. "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample."

104. The person of ordinary skill in the art would understand "detecting the presence of" to have its ordinary and customary meaning and does not need to be construed. If a construction is required, the person of ordinary skill in the art would understand this phrase to mean "discovering or determining the existence, presence, or fact of." They would also understand "paternally inherited nucleic acid of fetal origin" to mean "a nucleic acid that originated from the fetus and which was inherited from the father."

105. This limitation is practiced by the Aria Harmony Prenatal Test. As stated in the Aria AJOG publication:

> DANSR assay
>
> We designed DANSR assays against loci in the human genome as previously described. **To assess chromosome proportion, we designed assays against 576 non-polymorphic loci on each of chr18 and chr21**, where each assay consisted of three locus specific oligonucleotides: a left oligo with a 5' universal amplification tail, a 5' phosphorylated middle oligo, and a 5' phosphorylated right oligo with a 3' universal amplification tail. **To assess fetal fraction, we designed assays against a set of 192 SNP-containing loci on chr1-12**, where two middle oligos, differing by one base, were used to query each SNP. SNPs were optimized for minor allele frequency in the HapMap 3 dataset (http://hapmap.ncbi.nlm.nih.gov/). Oligonucleotides were synthesized by IDT and pooled together to create a single multiplexed DANSR assay pool.

Aria AJOG Publication at 6 (emphasis added), and:

> The slide was processed on an Illumina HiSeq 2000 to produce **a 56 base locus-specific sequence** and a 7 base sample tag sequence from an average of 1.18 million (M) clusters/sample. **Locus specific reads were compared to expected locus sequences. An average of 1.15M (97%) reads had fewer than 3 mismatches with expected locus sequences, resulting in an average of 854 reads/locus/sample.**

Aria AJOG Publication at 7 (emphasis added). This excerpt explains that the Illumina HiSeq 2000 DNA sequencer is used by Aria to obtain the nucleic acid sequence, i.e., the sequence of A, C, G, and T bases, for the amplified cfDNA from the sample. The sequences of the cfDNA from samples – the "Locus specific reads" – were then compared to "expected locus sequences." In other words, the sequences in the samples were identified by comparing them to the known sequences at the various loci.

106. The next part of the Aria process is to analyze all the sequences identified at the various loci. Aria uses two analyses for two different categories of loci: (1) analysis of non-polymorphic loci on chromosome 21 to determine the proportion of "sequence counts" for chromosome 21; and (2) analysis of polymorphic loci to determine the "fetal fraction." See paragraph 105 above, setting out the DANSR assays for the non-polymorphic and polymorphic loci.

(i) Aria's "Analysis of non-polymorphic loci for chromosome proportion"

107. In this analysis of non-polymorphic loci, Aria takes the nucleic acid sequence data from the HiSeq 2000 to determine sequence counts for the selected loci in chromosomes 21 and 18. The Aria AJOG Publication states that:

> **Sequence counts** were normalized by systematically removing sample and assay biases. Sequence counts follow a log normal distribution, so biases were estimated using median polish on log transformed counts. A chr21 proportion metric was then computed for each sample as the mean of **counts for selected chr21 loci** divided by the sum of the mean of counts for selected chr21 loci and the mean of counts for all 576 chr18 loci. A chr18 proportion metric was similarly calculated for each sample. A standard Z test of proportions was used to compute Z Statistics.

Aria AJOG Publication at 7 (emphasis added).

108. In conducting its chromosome proportion analysis, Aria is detecting the presence of nucleic acid sequences on chromosome 21. The nucleic acid sequences detected in a sample are from the mother and the fetus, and the sequences from the fetus are nucleic acid sequences inherited from the mother *and* nucleic acid sequences inherited from the father. Whether or not a sample is aneuploid, the detected nucleic acids include nucleic acids from the fetus which the

fetus inherited from its father. Thus, by determining the proportion of chromosome 21 (and 18), the Aria method detects nucleic acids inherited from the father, which are "paternally inherited nucleic acids of fetal origin."

109. Accordingly, in running the DANSR assay to obtain the chromosome proportion for chromosomes 21 and 18, Aria is practicing this limitation of claim 1.

(ii) Aria's "Analysis of polymorphic loci for fetal fraction"

110. In this analysis, Aria takes the nucleic acid sequence data from the HiSeq 2000 and analyses known polymorphic loci "where fetal alleles differ from maternal alleles" to determine the fraction of fetal DNA to total DNA in a sample. These fetal alleles that differ from maternal alleles will have come from the father. As stated in the Aria paper under the heading "DANSR assay":

> To assess fetal fraction, we designed assays against a set of 192 SNP-containing loci on chr1-12, where two middle oligos, differing by one base, were used to query each SNP. SNPs were optimized for minor allele frequency in the HapMap3 dataset…

Aria AJOG Publication at 6. What this means is that Aria chose the 192 SNPs to maximize the differences between the fetal alleles and the maternal alleles. The Aria publication later describes, under the heading "Analysis of polymorphic loci for fetal fraction":

> **Informative polymorphic loci were defined as loci where fetal alleles differ from maternal alleles.** Because DANSR exhibits allele specificities exceeding 99%, informative loci were readily identified when the fetal allele proportion of a locus was measured to be between 1 and 20%.

Aria AJOG Publication at 8 (emphasis added). The same publication further explains:

> **DANSR allowed us to develop an integrated assay to assess polymorphic as well as non-polymorphic loci, thereby permitting simultaneous determination of fetal fraction and chromosome proportion.** We used fetal fraction information by imposing a QC requirement that each sample have at least 3% fetal DNA, thereby avoiding low confidence calls arising from low proportions of fetal DNA.

Aria AJOG Publication at 14 (emphasis added).

111. Because the fetus inherits its chromosomes, *i.e.*, its nucleic acids, from the mother and the father, the "fetal alleles" that "differ from maternal alleles" will exist on a nucleic acid inherited from the father, *i.e.*, a paternally inherited nucleic acid of fetal origin. In other words, Aria detects "paternally inherited nucleic acids of fetal origin" in determining the "fetal fraction."

112. Moreover, according to the Aria AJOG publication, the "fetal fraction" is an essential feature of the Aria test:

> Importance of fetal fraction
>
> A principal determinant of the accuracy of any cfDNA analysis method is the fraction of fetal cfDNA in the sample. The higher the fraction of fetal cfDNA, the greater the difference in the number of cfDNA fragments originating from trisomic versus disomic chromosomes and hence the easier it is to detect trisomy. The FORTE algorithm explicitly accounts for fetal fraction in calculating trisomy risk.

Aria AJOG Publication at 16.

113. Thus, the analysis of the polymorphic loci in the Aria test, like the analysis of the non-polymorphic loci, detects paternally inherited nucleic acids of fetal origin, and this limitation of claim 1 of the '540 patent is met.

114. In sum, Aria's Harmony Prenatal Test that utilizes the DANSR and FORTE processes practices all the limitations of claim 1 and infringes claim 1 of the '540 patent.

B. CLAIM 2

1. "2. The method according to claim 1, wherein the foetal nucleic acid is amplified by the polymerase chain reaction."

115. The person of ordinary skill in the art understands that "the polymerase chain reaction," also referred to by its initials as "PCR," would have its ordinary and customary meaning in 1997 (as described above in paragraph 42).

116. The Aria Harmony Prenatal Test amplifies the fetal nucleic acid by the polymerase chain reaction. As stated in the Aria AJOG publication:

> 8mL blood per subject was collected into a Cell-free DNA tube (Streck) and stored at room temperature for up to 3 days. Plasma was isolated from blood via double centrifugation and stored at -20C for up to a year. cfDNA was isolated from plasma using Viral NA DNA purification beads (Dynal),

> biotinylated, immobilized on MyOne C1 streptavidin beads (Dynal), and annealed with the multiplexed DANSR oligonucleotide pool. **Appropriately hybridized oligonucleotides were catenated with Taq ligase, eluted from the cfDNA, and amplified using universal PCR primers. PCR product from 96 independent samples was pooled** and used as template for cluster amplification on a single lane of a TruSeq v2 SR flow slide (Illumina). …

Aria AJOG Publication at 7 (emphasis added). This publication states that the fetal nucleic acid is amplified by PCR. See also Figure 1 of the Aria AJOG Publication, which also shows that the fetal nucleic acid is amplified by PCR.

117. Accordingly, the Aria Harmony Prenatal Test infringes claim 2 of the '540 patent.

C. CLAIM 8

1. **"8. The method according to claim 1, wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected."**

118. The person of ordinary skill in the art would understand "foetal nucleic acid from a paternally-inherited non-Y chromosome" to have its ordinary and customary meaning of "a nucleic acid that originated from the fetus which was inherited from the father and which is not from the Y chromosome."

119. According to the Aria AJOG Publication, the fetal nucleic acids detected by Aria in the Harmony Prenatal Test are from chromosomes 18 and 21 and from chromosomes 1 to 12 (see paragraph 105 above), and not from the Y chromosome. That is, Aria's Harmony Prenatal Test detects "the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome."

120. Accordingly Aria's Harmony Prenatal Test infringes claim 8 of the '540 patent.

D. CLAIM 19

1. **"19. The method according to claim 1, wherein the sample contains foetal DNA at a fractional concentration of total DNA of at least about 0.14%, without subjecting it to a foetal DNA enrichment step."**

121. The person of ordinary skill in the art in 1997 would understand the ordinary and customary meaning of "fractional concentration" to be the fraction of the total. The person of ordinary skill in the art would also understand "foetal DNA enrichment" to have its ordinary and

customary meaning of "increasing the concentration of fetal DNA relative to the maternal DNA in the sample."

122. According to Aria's AJOG Publication, Aria imposes a quality control requirement that samples must have at least 3% fetal DNA:

> We used fetal fraction information by imposing **a QC requirement that each sample have at least 3% fetal DNA**, thereby avoiding low confidence calls arising from low proportions of fetal DNA.

Aria's AJOG Publication at 14 (emphasis added). This means that Aria's method tests samples in which the fetal DNA is at a fractional concentration of at least 3%, which meets the claim limitation of "at least about 0.14%." *See also* Aria's AJOG Publication at 11 which states that a number of samples in the training set that did not meet the "QC criteria" – including where "**fetal fraction <3%**" – "were removed from the dataset."

123. In addition, based on the description of the DANSR assay in the Aria AJOG Publication and the Aria PD Publication, the DANSR assay does not have a step of increasing the concentration of fetal DNA relative to the maternal DNA, and hence does not include a "foetal DNA enrichment step."

124. Accordingly, Aria's Harmony Prenatal Test infringes claim 19 of the '540 patent.

E. CLAIM 20

1. "20. The method according to claim 19, wherein the fractional concentration of foetal DNA is at least about 0.39%."

125. For the same reasons that Aria's Harmony Prenatal Test infringes claim 19, it also infringes claim 20 because the fractional concentration of fetal DNA is at least 3% in the Aria test, which is "at least about 0.39%."

F. CLAIM 21

1. "21. A method of performing a prenatal diagnosis, which method comprises the steps of:"

126. I understand that this is a "preamble" and therefore not generally a claim limitation. If, however, it were to be construed as a claim limitation, the person of ordinary skill in the art would understand that the '540 patent defines "prenatal diagnosis" as follows:

> The term "prenatal diagnosis" as used herein covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or to the quantity or quality of the foetal DNA in the maternal serum or plasma. Included are sex determination, and detection of foetal abnormalities which may be for example chromosomal aneuploidies or simple mutations. Also included is detection and monitoring of pregnancy-associated conditions such as pre-eclampsia which result in higher or lower than normal amounts of foetal DNA being present in the maternal serum or plasma. The nucleic acid detected in the method according to the invention may be of a type other than DNA e.g. mRNA.

'540 patent at 2:6-18. According to Aria's Press Release, its Harmony Prenatal Test is "a directed noninvasive approach to cell-free DNA (cfDNA) analysis in maternal blood to detect common trisomies linked to genetic disorders." This is a "prenatal diagnosis" according to the definition of the '540 patent.

2. "(i) providing a maternal blood sample;"

127. The Aria Harmony Prenatal Test involves "providing a maternal blood sample." The person of ordinary skill in the art would understand "providing a maternal blood sample" to mean "supplying or making available a blood sample from a pregnant female." The Merriam-Webster on-line dictionary defines "provide" as "supply or make available (something wanted or needed)."

128. The Aria AJOG Publication states: "8mL blood per subject was collected into a Cell-free DNA tube (Streck) and stored at room temperature for up to 3 days." Aria AJOG Publication at 7. In the course of receiving a blood sample to be tested, Aria clearly makes it available, i.e., "provides" the maternal blood sample to its laboratory personnel who actually conduct the testing. Therefore, Aria meets this element of claim 21.

3. "(ii) separating the sample into a cellular and a non-cellular fraction;"

129. The person of ordinary skill in the art would understand that "separating the sample into a cellular and a non-cellular fraction" has its ordinary and customary meaning. By separating out the plasma, which is a "non-cellular fraction," from the rest of the maternal blood sample (see paragraph 100 above), the Aria Harmony Prenatal Test meets this step.

4. "(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;"

130. As described for claim 1 (in paragraphs 104-113 above), the Aria Harmony Prenatal Test "detects the presence of a nucleic acid of foetal origin in the non-cellular fraction," the "non-cellular fraction" being the plasma extracted from the maternal blood sample. Accordingly, the Aria Harmony Prenatal Test meets this step.

5. "(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid."

131. As explained above in relation to the preamble of claim 21, the Aria Harmony Prenatal Test is "a directed noninvasive approach to cell-free DNA (cfDNA) analysis in maternal blood to detect common trisomies linked to genetic disorders." This is a "prenatal diagnosis" according to the definition of the '540 patent. Moreover, as also explained in paragraphs 104-113 above, the Aria Harmony Prenatal Test detects the presence of fetal nucleic acid, and quantity of fetal nucleic acid (via the "fetal fraction"), and sequence of fetal nucleic acid (via the "reads" from the Illumina HiSeq 2000), upon each of which the diagnosis is based. Accordingly, the Aria Harmony Prenatal Test meets this step as well.

132. In sum, the Aria Harmony Prenatal Test meets all the limitations of claim 21 and therefore infringes claim 21 of the '540 patent.

G. CLAIM 22

1. "22. The method according to claim 21, wherein the non-cellular fraction as used in step (iii) is a plasma fraction."

133. As explained for claim 21 above, the Aria Harmony Prenatal Test uses plasma, which is a non-cellular fraction, separated from the rest of the maternal blood sample. Accordingly, the Aria Harmony Prenatal Test infringes claim 22 of the '540 patent.

H. CLAIM 24

1. "24. A method for detecting a paternally inherited nucleic acid on a maternal blood sample, which method comprises:"

134. This element is the "preamble" for claim 24 and I understand that it is therefore generally non-limiting. In any event, even if it is determined by the Court to be a limitation, as explained for claim 1 above, the Aria Harmony Prenatal Test is a "method for detecting a paternally inherited nucleic acid on [sic: in] a maternal blood sample."

2. "removing all or substantially all nucleated and anucleated cell populations from the blood sample,"

135. The person of ordinary skill in the art would understand that this step of "removing all or substantially all nucleated and anucleated cell populations from the blood sample" is performed by separating out the plasma fraction from the maternal blood sample. The "nucleated" (which means with a nucleus) and "anucleated" (which means not having a nucleus) "cell populations" form the non-plasma fraction of the blood sample, which is not used.

136. Accordingly, this step is met by the Aria Harmony Prenatal Test in which the plasma fraction of the maternal blood sample is separated from the maternal blood sample.

3. "amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally inherited fetal nucleic acid."

137. The person of ordinary skill in the art would understand "subjecting the amplified nucleic acid to a test for the Paternally inherited fetal nucleic acid" to be given its ordinary and customary meaning, which would include, at least, "performing an analysis to detect the paternally inherited fetal nucleic acid."

138. As already described in paragraphs 98-103 above, the Aria Harmony Prenatal Test involves amplifying the cell-free nucleic acid, which includes "paternally inherited nucleic acid," in the plasma fraction, which is "the remaining fluid."

139. Then, as also described in paragraphs 104-113 above, in the Aria Harmony Prenatal Test the amplified nucleic acid is processed on the Illumina HiSeq 2000 to detect, i.e., "test for," the paternally inherited fetal nucleic acid. Thus, this step of claim 24 is also met.

140. In sum, the Aria Harmony Prenatal Test infringes claim 24 of the '540 patent.

I. CLAIM 25

1. "25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises "

141. As already described above for claim 1, the Aria Harmony Prenatal Test is a "method for performing a prenatal diagnosis on a maternal blood sample." Hence whether or not this is a limitation of claim 25 or just a non-limiting preamble, it is practiced by the Aria Harmony Prenatal Test.

2. "obtaining a non-cellular fraction of the blood sample"

142. As described in paragraph 100 above, the Aria Harmony Prenatal Test uses the plasma fraction of the blood sample. The plasma fraction is a "non-cellular fraction" and hence this step is met.

3. "amplifying a paternally inherited nucleic acid from the non-cellular fraction"

143. As described in paragraphs 98-103 above, the Aria Harmony Prenatal Test amplifies the nucleic acid in the plasma, *i.e.*, "non-cellular" fraction, of the blood sample. The nucleic acid that is amplified includes the "paternally inherited nucleic acid" and hence this step is met by the Aria Harmony Prenatal Test.

4. "and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid."

144. Finally, as again described in paragraphs 104-113 above, the Aria Harmony Prenatal Test uses the Illumina HiSeq 2000 to "perform analysis" on the amplified nucleic acid and "detect" the "paternally inherited fetal nucleic acid." Accordingly, this step of claim 25 is also practiced by the Aria Harmony Prenatal Test.

145. In sum, the Aria Harmony Prenatal Test meets all the limitations of claim 25, and therefore infringes claim 25 of the '540 patent.

X. PRESUMPTION OF VALIDITY OF THE '540 PATENT

146. I am informed and understand that it is not Sequenom's burden to prove the validity of the asserted claims of the '540 patent. I am informed and understand that a patent is presumed valid. I also understand that Aria has not challenged the validity of the '540 patent in

its complaint for a declaratory judgment of non-infringement. If Aria offers any arguments or evidence relating to validity, I reserve the right to respond by way of a supplemental declaration.

XI. POTENTIAL HARM TO THE MARKET FOR NONINVASIVE PRENATAL TESTING FROM ARIA'S HARMONY PRENATAL TEST

147. In this section, I explain briefly my opinion that if Aria is permitted to market the Aria Harmony Prenatal Test™ at all, *i.e.*, if it is not enjoined, and if it markets the test to women with low risk of fetal aneuploidy pregnancies without a proper clinical validation, it will significantly harm the market for noninvasive aneuploidy testing.

A. INDICATED USES FOR SEQUENOM'S MATERNIT21™ TEST AND ARIA'S HARMONY PRENATAL TEST

148. I understand that Mr. William Welch of Sequenom states in his declaration that:

> The MateriT21 test is indicated for use in pregnant women who are at increased risk (by medical and clinical indicators) of carrying a fetus with Down syndrome or trisomies 18 or 13, including women who will be over age 35 at term, have a suspicion of problematic pregnancy indicated by a positive serum screening result, a positive ultrasound result or prior affected pregnancy or family history. In the United States, there are an estimated 750,000 such high–risk pregnancies each year.

Welch Declaration at ¶13. I understand that Mr. Welch further states that:

> Sequenom has initially focused on the high risk group because our clinical data is derived from clinical studies of women in the high risk group. Sequenom intends to expand the test's coverage to include lower risk group if and when supported by clinical data from further studies.

Id, footnote 2.

149. I have also reviewed a copy of Aria's marketing materials relating to its Harmony Prenatal Test™, a copy of which is attached as Exhibit 9. In contrast to Sequenom's MateriT21™ test, there is no indication in the Aria marketing materials that the Aria test is limited to women in the high-risk group. Rather, the Aria marketing materials state:

> Who can get the Harmony Prenatal Test?
>
> The Harmony Prenatal Test service can be ordered by healthcare professionals for women with pregnancies of at least 10 weeks' gestational

age. The test is not for use in multiple pregnancies (such as twins) or egg-donor pregnancies.

Exhibit 9 at page 5. Significantly, although Aria excludes use of its test for multiple pregnancies and egg-donor pregnancies, it does not exclude use of its test for non-high-risk pregnancies.

150. However, the only clinical data identified by the Aria marketing materials relates to women with high-risk pregnancies. *See* Exhibit 9 at page 8. The larger clinical trials that may include women outside the high-risk group are still "enrolling," indicating that no actual data has yet been obtained. This is significant because it is important that tests are only indicated for use on populations for whom proper clinical validation has been conducted to confirm the effectiveness of the test.

151. It is common practice, and very good sense, to start new technologies in high risk groups. Only after the community becomes comfortable with the benefits and limitations of a new approach is it reasonable to expand to a low risk population for whom, by definition the performance will be poorer.

B. ARIA'S TEST WOULD CAUSE HARM TO THE MARKET FOR NONINVASIVE PRENATAL TESTING

152. This is precisely the problem with administering the Aria test to women outside the "high risk" group when there are not sufficient clinical data to support its effectiveness for that group. The published clinical data thus far indicate that the Aria test would be appropriate only for women at high risk of carrying a fetus with Down syndrome.

153. The Ashoor paper, which describes a small clinical study involving the Aria test, considers the "extent to which cfDNA [*i.e.*, cell-free DNA] analysis could also be applied as a universal screening tool for trisomy 21." (Exhibit 7, Ashoor, at page 13.) It states that "[i]t would also be necessary to demonstrate that the observed accuracy with cfDNA testing obtained from the investigation of pregnancies at high-risk for aneuploidies is applicable to the general population where the prevalence of fetal trisomy 21 is much lower. This may well prove to be the case because the ability to detect aneuploidy with cfDNA is dependent upon assay precision and

fetal DNA percentage in the sample rather than the prevalence of the disease in the study population." *Id*. at 13-14.

154. The Ashoor paper also states that "further research is needed to firstly, investigate the accuracy of the [Aria] test in intermediate- and low-risk pregnancies… ." (Exhibit 7, Ashoor, at page 14.) I am surprised therefore that, despite this recognition of the need for more investigation, the Aria marketing materials do not limit the proposed use of the Aria test to high-risk pregnancies.

155. If Aria is permitted to market the Harmony Prenatal Test™ at all, *i.e.*, if it is not enjoined, and if it markets the test to women with low risk of fetal aneuploidy pregnancies without a proper clinical validation, it will significantly harm the market for noninvasive aneuploidy testing.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed on March 8, 2012 in Fort Lee, New Jersey.

/s/ Dr. Mark I. Evans
Dr. Mark. I. Evans

I Michael Malecek, the ECF filer of this document hereby attest that I have on file all holograph signatures for any signatures indicated by a "conformed" signature (/s/) within this efiled document.